

## REMARKS

1. All outstanding requirements will now be addressed in the order they appear in the Office Action mailed September 16, 2011.

### *Claim Rejections - 35 USC § 112*

2. Claim 1 stands rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such as reagents, solvents and conditions etc. The Examiner states that Applicant has limited the alkylation to be N-alkylation but without the required reagent of benzylbromide, and that the particular alkylated product has not been pointed out.

In response, Applicant has amended claim 1 without prejudice to specify that the reactant used to react with the compound of formula (IV) in the N-alkylation reaction in c) is a compound of formula Y-(CH<sub>2</sub>)<sub>n+1</sub>R<sup>5</sup>, wherein Y represents a chlorine atom, a bromine atom, or an iodine atom, R<sup>5</sup> represents a phenyl or a substituted phenyl; and n is 0.

Withdrawal of the rejection to claim 1 is respectfully requested.

3. Claims 1-6, 12, 15-20, 22-28, 31 stand rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner states that among the various starting materials of formula (II) or formula (III), only the compounds wherein R<sup>2</sup> and R<sup>3</sup> represents H, F, C<sub>1-4</sub> alkyl or C<sub>1-4</sub> alkoxy are available at the time the invention was made.

Without acquiescing in this rejection, Applicant has amended claim 1 without prejudice to claim that R<sup>1</sup> and R<sup>4</sup> independently represent H, R<sup>2</sup> and R<sup>3</sup> independently represent H, F, an alkyl having from 1 to 4 carbon atoms, or an alkoxy having from 1 to 4 carbon atoms.

Withdrawal of the rejection to claims 1-6, 12, 15-20, 22-28, 31 is respectfully requested.

***Claim Rejections – 35 USC § 102***

**4.** Claims 1-6, 15-28, and 30-33 stand rejected under 35 U.S.C. 102(e) as being anticipated by Kumar et al. (WO 04/082685) (“Kumar”).

In response, Applicant respectfully submits that Kumar is not a prior reference against this Application because Applicant had invented this invention before the application for patent in the United States by Kumar. Applicant submits herewith a declaration of inventor Hesheng ZHANG under 37 C.F.R. § 1.131 to establish prior completion of the invention as claimed in the pending claims by Applicant.

In light thereof, reconsideration and withdrawal of the 102(e) rejection is respectfully requested.

***Claim Rejections – 35 USC § 103***

**5.** Claims 1-6, 12, and 15-33 stand rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over Kumar in view of Lensky (U.S. Pat. 5,606,064).

In response, Applicant respectfully submits that at least Kumar is not a prior reference against this Application because Applicant had invented this invention before the application for patent in the United States by Kumar. Applicant submits herewith a declaration of inventor Hesheng ZHANG under 37 C.F.R. § 1.131 to establish prior completion of the invention as claimed in the pending claims by Applicant.

In light thereof, reconsideration and withdrawal of the 103(a) rejection is respectfully requested.

**6.** Claims 1-2, 4-6, 12, 15-33 stand rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over Lensky (U.S. Pat. 5,606,064) in view of Devries ‘584 (WO 97/22584). The

Examiner alleges that Lensky recites “very similar steps” except that “instead of alkylation being performed at the last step, it was performed before hydrogenation”. The Examiner further alleges that since Devries ‘584 discloses alkylation after hydrogenation, changing the sequence of steps would have been obvious.

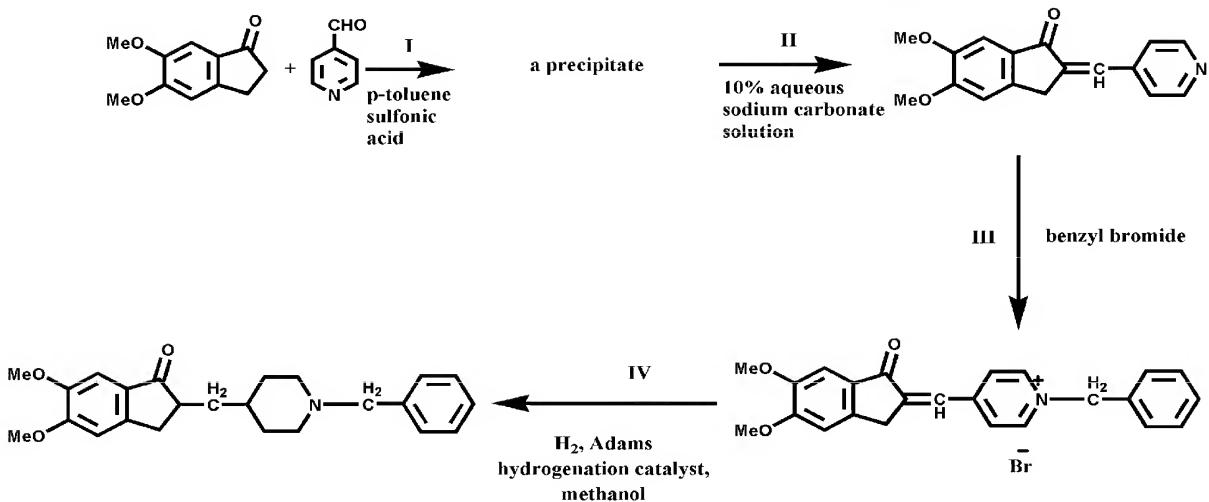
In response, Applicant respectfully requests reconsideration of the claims as amended. Arguments presented below also apply to the newly added claim 34.

The factual determinations underpinning the legal conclusion of obviousness include: 1) the scope and content of the prior art, 2) the level of ordinary skill in the art, 3) the differences between the claimed invention and the prior art, and 4) evidence of secondary factors, also known as objective indicia of non-obviousness. See, Esai Co., Ltd. v. Dr. Reddy's Laboratories, Ltd., 533 F.3d 1353 (Fed. Cir. 2008) citing Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966).

#### The Scope and Content of the Prior Art

#### Lensky

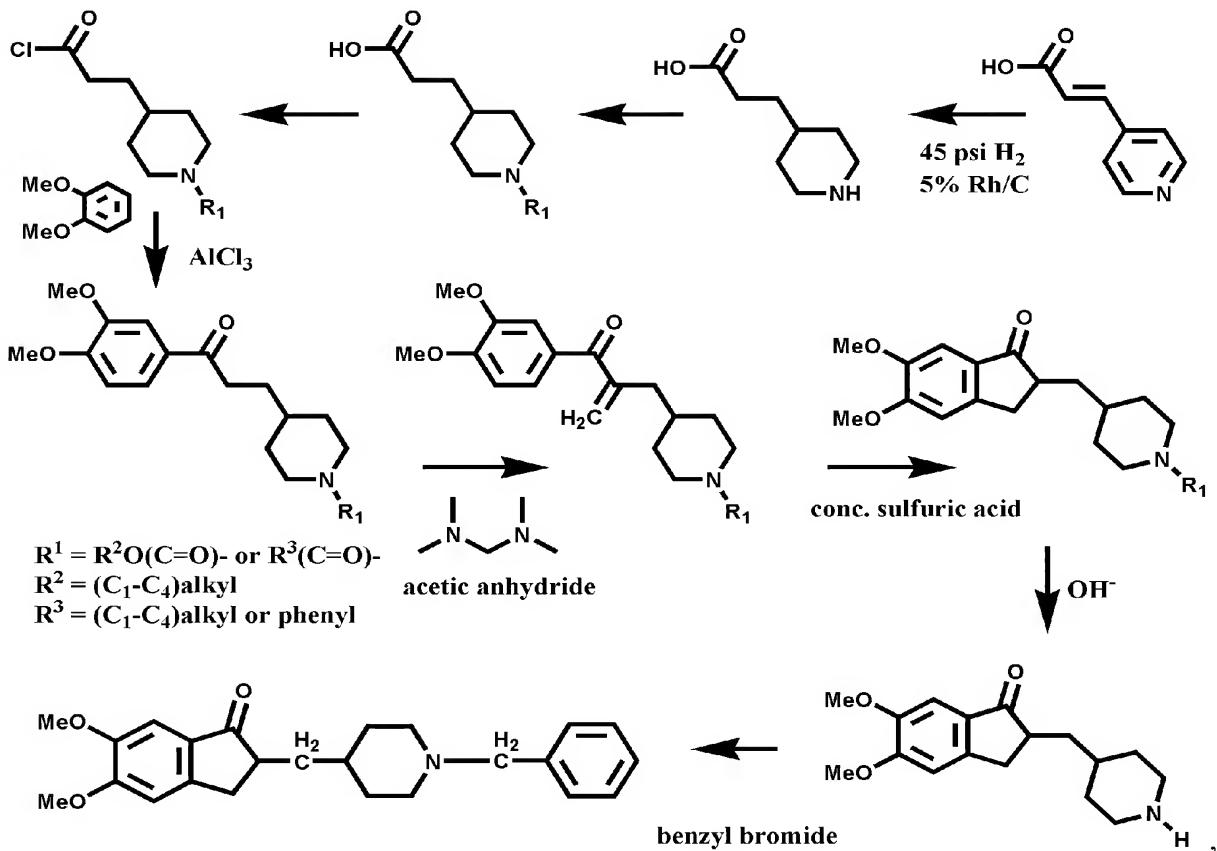
Lensky recites a process for the preparation of denepezil, as illustrated below in **Scheme I**, including: I) reacting 5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one with pyridine-4-aldehyde in the presence of p-toluenesulphonic acid to yield a precipitate; II) stirring the precipitate in 10% sodium carbonate solution to obtain 5,6-dimethoxy-2-(pyridin-4-ylmethylene)-2,3-dihydro-1*H*-inden-1-one; III) reacting 5,6-dimethoxy-2-(pyridin-4-ylmethylene)-2,3-dihydro-1*H*-inden-1-one with benzyl bromide to form 1-benzyl-4-((5,6-dimethoxy-1-oxo-1*H*-inden-2(3*H*)-ylidene)methyl)pyridinium bromide, and IV) hydrogenating 1-benzyl-4-((5,6-dimethoxy-1-oxo-1*H*-inden-2(3*H*)-ylidene)methyl)pyridinium bromide to form 2-((1-benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one.



**Scheme I**

Devries '584

Devries '584 recites a process for the preparation of donepezil, as illustrated below in **Scheme II**, including: a) hydrogenating 3-pyridin-4-ylpropen-2-oic acid to yield 3-piperidin-4-ylpropanoic acid, (b) reacting 3-piperidin-4-ylpropanoic acid with methyl chloroformate to yield 3-[N-(Methoxycarbonyl)-piperidin-4-yl]propionic acid; c) converting 3-[N-(Methoxycarbonyl)-piperidin-4-yl]propionic acid to 4-(2-chlorocarbonyl-ethyl)-piperidine-1-carboxylic acid methyl ester; d) reacting 4-(2-chlorocarbonyl-ethyl)-piperidine-1-carboxylic acid methyl ester with 1,2-dimethoxybenzene in the presence of aluminum chloride to 4-[3-(3,4-dimethoxy-phenyl)-3-oxo-propyl]-piperidine-1-carboxylic acid methyl ester; e) converting 4-[3-(3,4-dimethoxy-phenyl)-3-oxo-propyl]-piperidine-1-carboxylic acid methyl ester to 4-[2-(3,4-dimethoxy-benzoyl)-allyl]-piperidine-1-carboxylic acid methyl ester; f) converting 4-[2-(3,4-dimethoxy-benzoyl)-allyl]-piperidine-1-carboxylic acid methyl ester to 4-(5,6-dimethoxy-1-oxo-indan-2-ylmethyl)-piperidine-1-carboxylic acid methyl ester; g) converting 4-(5,6-dimethoxy-1-oxo-indan-2-ylmethyl)-piperidine-1-carboxylic acid methyl ester with potassium hydroxide to yield 5,6-dimethoxy-2-piperidin-4-ylmethyl-indan-1-one; and h) reacting 5,6-dimethoxy-2-piperidin-4-ylmethyl-indan-1-one with benzyl bromide to yield 2-(1-benzyl-piperidin-4-ylmethyl)-5,6-dimethoxy-indan-1-one.



**Scheme II**

The Level of Ordinary Skill in the Art

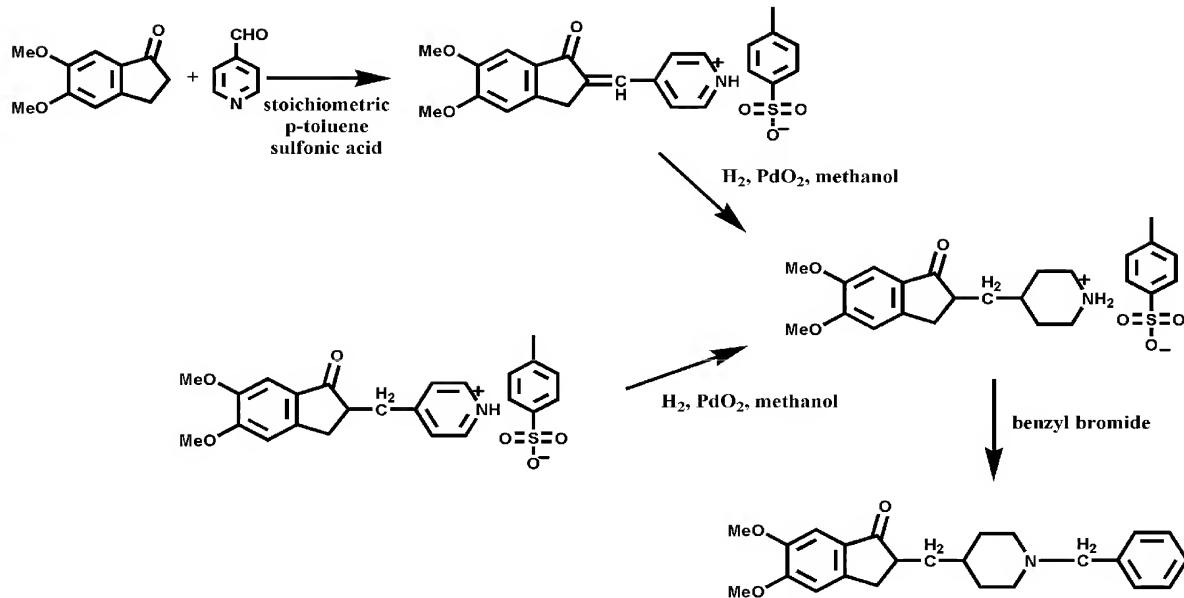
A person of ordinary skill in the art with respect to the invention is a chemist. Ordinary level of skill in chemical arts, and particularly in chemical arts dealing with developing new chemical processes is relatively low. In general, and apart from special circumstances, chemists cannot accurately and unambiguously predict outcomes of chemical reactions without undue experimentation, especially those chemical reactions that involve complex chemical compounds having multiple functional groups. This is to say also that the chemical arts are often unpredictable. See, e.g., *Eisai* at 1359 (Fed. Cir. 2008) (“To the extent an art is unpredictable, as the chemical arts often are [...]”).

The Differences between the Claimed Invention and the Related Art

Because the references at issue recite chemical compounds that undergo chemical reactions, the analysis of the differences between the claimed invention and the prior art turns here *inter alia* on the structural similarities and differences between compounds used in the claimed process and compounds used in processes recited in the references cited. Cf, Eisai at 1359 (Fed. Cir. 2008) quoting Eli Lilly & Co. v. Zenith Goldline Pharms., Inc., 471 F.3d 1369, 1377 (Fed. Cir. 2006) (noting that, for a chemical compound, a *prima facie* case of obviousness requires “structural similarity between claimed and prior art subject matter ... where the prior art gives reason or motivation to make the claimed compositions” (quoting In re Dillon, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc))).

Obviousness based on structural similarity of a chemical process thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known process in a particular way to achieve the claimed process. Cf, Eisai at 1359 (Fed. Cir. 2008) quoting Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356 (Fed. Cir. 2007).

Applicant’s process for the preparation of denepezil as shown in **Scheme III** (below), comprises: a) reacting 5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one and pyridine-4-carboxaldehyde in the presence of a stoichiometric amount of p-toluene sulfonic acid to obtain **4-((5,6-dimethoxy-1-oxo-1*H*-inden-2(3*H*)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate**; b) reducing **4-((5,6-dimethoxy-1-oxo-1*H*-inden-2(3*H*)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate** or **5,6-dimethoxy-2-(4-pyridyl)methyl-indan-1-one 4-methylbenzenesulfonic acid** with H<sub>2</sub> using PtO<sub>2</sub> in methanol to afford **4-((5,6-dimethoxy-1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl)piperidinium 4-methylbenzenesulfonate**; and c) reacting **4-((5,6-dimethoxy-1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl)piperidinium 4-methylbenzenesulfonate** with benzyl bromide in the presence of a base to yield **2-((1-benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one**.



**Scheme III**

The differences between Applicant's process as claimed and the process recited in Lensky lie at least in that:

- 1) Lensky recites reacting 5,6-dimethoxy-indan-1-one with pyridine-4-carboxaldehyde to obtain **5,6-dimethoxy-2-(pyridine-4-yl)methylene-indan-1-one**, which undergoes subsequent proceeding. In Applicant's process, it is **4-((5,6-dimethoxy-1-oxo-1H-inden-2(3H)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate** that undergoes hydrogenation directly.

In Lensky, 5,6-dimethoxy-indan-1-one is reacted with pyridine-4-carboxaldehyde in the presence of p-toluene sulfonic acid to obtain a precipitate, then the precipitate is stirred with 10% aqueous sodium carbonate solution to obtain 5,6-dimethoxy-2-(pyridine-4-yl)methylene-indan-1-one. Applicant respectfully submits that any **4-((5,6-dimethoxy-1-oxo-1H-inden-2(3H)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate** formed in Lensky's

process is basified using 10% aqueous sodium carbonate solution and immediately converts to the free 5,6-dimethoxy-2-(pyridin-4-ylmethylene)-2,3-dihydro-1*H*-inden-1-one.

It is well-known to a skilled person that p-toluene sulfonic acid plays the role of a catalyst in the reaction of 5,6-dimethoxy-indan-1-one with pyridine-4-carboxaldehyde to produce 5,6-dimethoxy-2-(pyridine-4-yl)methylene-indan-1-one. Before this invention was made, a person with ordinary skill in the art would not have known that p-toluene sulfonic acid reacts with 5,6-dimethoxy-indan-1-one and pyridine-4-carboxaldehyde to produce a tosylate salt. Hereto, please see the enclosed declaration under 37 C.F.R. § 1.132 of inventor Hesheng ZHANG.

There is no mention in Lensky that 4-((5,6-dimethoxy-1-oxo-1*H*-inden-2(3*H*)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate is formed. A skilled artisan referring Lensky thus would not have known it is beneficial to hydrogenate 4-((5,6-dimethoxy-1-oxo-1*H*-inden-2(3*H*)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate directly. A skilled artisan thus would not have been motivated to hydrogenate 4-((5,6-dimethoxy-1-oxo-1*H*-inden-2(3*H*)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate directly without further converting it to the neutral 5,6-dimethoxy-2-(pyridine-4-yl)methylene-indan-1-one, which is formed in the process of Lensky for further processing.

2) In Lensky, 5,6-dimethoxy-2-(pyridine-4-yl)methylene-indan-1-one is firstly alkylated and the obtained alkylation product is hydrogenated, while in Applicant's process, it is 4-((5,6-dimethoxy-1-oxo-1*H*-inden-2(3*H*)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate that is hydrogenated first and the obtained hydrogenation product is then alkylated.

Applicant respectfully submits that the Applicant's process differs from Lensky not only in that the sequence of the alkylation step and the hydrogenation step is changed, but also in that the chemical intermediates involved are different. In Lensky, the involved intermediates are **5,6-dimethoxy-2-(pyridine-4-yl)methylene-indan-1-one** and 1-benzyl-4-((5,6-

dimethoxy-1-oxo-1H-inden-2(3H)-ylidene)methyl)pyridinium bromide, while in Applicant's process, the involved intermediates are two tosylates, ***4-((5,6-dimethoxy-1-oxo-1H-inden-2(3H)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate*** and ***4-((5,6-dimethoxy-1-oxo-2,3-dihydro-1H-inden-2-yl)methyl)piperidinium 4-methylbenzenesulfonate***.

There is no motivation that flows from Lensky for a skilled artisan to modify the intermediate ***5,6-dimethoxy-2-(pyridine-4-yl)methylene-indan-1-one*** as ***4-((5,6-dimethoxy-1-oxo-1H-inden-2(3H)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate*** because a skilled artisan would not have known the existence or possibility of obtaining this tosylate after reading Lensky. There is also no motivation for a skilled artisan to change the sequence of the alkylation step and the hydrogenation step in Lensky, because harsher hydrogenation conditions would be needed to reduce ***5,6-dimethoxy-2-(pyridine-4-yl)methylene-indan-1-one*** in a single step due to the conjugated system formed between the C=C bond and the pyridinyl ring, and lower yields would likely be obtained when the hydrogenation step is performed before the alkylation step. There is no motivation for a skilled artisan to change the sequence of the alkylation step and the hydrogenation step further because a skilled artisan would not have known that the C=C bond and the pyridinyl ring of ***4-((5,6-dimethoxy-1-oxo-1H-inden-2(3H)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate*** can be reduced via a single-step hydrogenation process.

Similarly, the differences between the present process and Devries '584 are large. In Devries '584, hydrogenation occurs at the stage of 3-pyridin-4-ylpropen-2-oic acid rather than as in Applicant's process at the stage of ***4-((5,6-dimethoxy-1-oxo-1H-inden-2(3H)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate***. 3-pyridin-4-ylpropen-2-oic acid is chemically much different from ***4-((5,6-dimethoxy-1-oxo-1H-inden-2(3H)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate***. The former is an alfa, beta-unsaturated carboxylic ***acid*** conjugated to an aromatic pyridine ring, while the latter is a tosylate ***salt*** of an indanone conjugated to a pyridinium cation. Because the reactivities of the two species are much different, a skilled artisan would not have been able to conclude after reading Devries '584 that ***4-((5,6-dimethoxy-1-oxo-1H-inden-2(3H)-***

ylidene)methyl)pyridinium 4-methylbenzenesulfonate could be successfully hydrogenated. In addition, while Devries '584 hydrogenates 3-pyridin-4-ylpropen-2-oic acid using rhodium on carbon Applicant uses platinum or palladium, and while Devries '584 uses 45 psi hydrogen pressure, Applicant uses less than 15 psi. Since the hydrogenation process of Devries '584 is much different from Lensky, there is no motivation and no expectation of success to modify the process by Lensky as proposed by the Examiner to arrive at the process as claimed by Applicant.

In sum, since neither Lensky nor Devries discloses 4-((5,6-dimethoxy-1-oxo-1H-inden-2(3H)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate, neither Lensky nor Devries teaches or suggests that the C=C bond and the pyridinyl ring of 4-((5,6-dimethoxy-1-oxo-1H-inden-2(3H)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate can be reduced via a single-step hydrogenation process, the Examiner has relied on hindsight to combine Lensky and Devries to conclude that the sequence of the alkylation step and the hydrogenation step could be changed and Applicant's *4-((5,6-dimethoxy-1-oxo-1H-inden-2(3H)-ylidene)methyl)pyridinium 4-methylbenzenesulfonat* can undergo a single step of hydrogenation to reduce the C=C bond and the pyridinyl ring. However, using hindsight is not permissible in making a prior art rejection, and the rejection should be withdrawn. See, *In re Fritch*, 972 F.2d 1260, 23 USPQ2d 1780 (Fed. Cir. 1992) ("It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious").

In light thereof, Applicant respectfully submits that a skilled artisan after reading Lensky and Devries would not have been motivated to modify the method recited therein to arrive at Applicant's invention as claimed. Reconsideration and withdrawal of the obviousness rejections over the claims as amended are respectfully requested.

Evidence of Secondary Factors

Applicant respectfully submits that the product in the first step of the present process is a tosylate, which allows the salt to precipitate out at the completion of the reaction. The neutralization and extraction steps, both of which are required in Lensky, are not necessary and are not used in Applicant's process and the solvent can be reused. Applicant's process is thus simpler.

It is unexpected that the yield of denepezil prepared according to Applicant's process is higher than that of Lensky. Hereto, please see the enclosed declaration under 37 C.F.R. §1.132 of inventor Hesheng ZHANG. Applicant's process for preparation of denepezil has a yield as high as 85% while in Lensky the yield is only 58%. This about 30% difference in yields is clearly superior and unexpected and heavily weighs in favor of finding Applicant's process non-obvious.

In light thereof, Applicant respectfully requests withdrawal of the obviousness rejections.

Claim 34

Claim 34 differs from claims 1, 23-25 in that Applicant has claimed that the compound of formula (IV) is obtained through the catalytic hydrogenation of the compound of formula (III), and that the hydrogenation process can proceed at room temperature and at a pressure of one atmosphere of H<sub>2</sub>. These limitations further distinguish from Lensky and Devries '584.

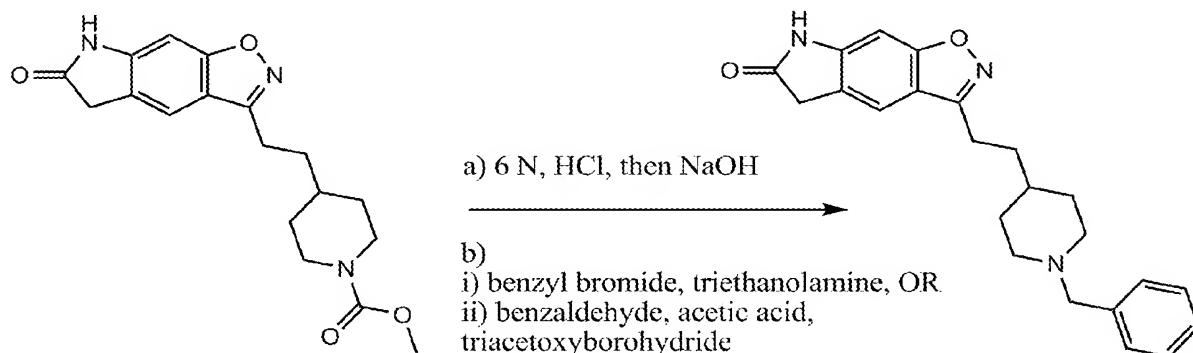
7. Claims 1-6, 12, 15-33 stand rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over Lensky in view of Devries '584 (WO 97/22584) and further in view of Devries et al. (U.S. Pat. No. 5,916,902) ("Devries '902").

The Examiner alleges that Lensky recites "very similar steps" except that "instead of alkylation being performed at the last step, it was performed before hydrogenation." However, the Examiner further alleges that since Devries '584 discloses alkylation after hydrogenation, and since Devries '902 suggested that N-benzylation can be carried out by a

benzylating agent or benzaldehyde in the presence of a reducing agent, changing the sequence of steps would have been obvious.

In response, Applicant respectfully requests reconsideration of the claims as amended. Arguments presented below also apply to the newly added claim 34.

Applicant re-alleges the arguments made in item 6 above. Further, Applicant respectfully submits that after considering Devries '902 in addition to Lensky and Devries '584, a skilled artisan would still not have arrived at Applicant's invention because Devries '902 applies a benzyl halide and a base or benzaldehyde in the presence of a reducing agent to much different intermediate than the one used in the processes claimed by Applicant. Specifically, as illustrated below in **Scheme 5**, Devries '902 converts an 5H-isoxazolo[4,5-f]indol-6(7H)-one rather than a 2,3-dihydro-1H-inden-1-one.



**Scheme 5**

There is no mention anywhere in the references cited that substituting the 5H-isoxazolo[4,5-f]indol-6(7H)-one of Devries '902 for the 2,3-dihydro-1H-inden-1-one core of Lensky would be beneficial.

In addition, Devries '902 does not use H<sub>2</sub> as a hydrogenation reagent, and Devries '902 does not suggest that H<sub>2</sub> could be used in situ with benzyl bromide. Thus, there is no motivation

and no expectation of success to modify the process by Lensky as proposed by the Examiner to arrive at the process as claimed by Applicant.

In light thereof, Applicant respectfully requests reconsideration and withdrawal of the obviousness rejections over the claims as amended.

***CONCLUSION***

In view of the foregoing amendments and remarks, Applicant submits that all pending claims are in condition for allowance and requests the issuance of a Notice of Allowance. Should an extension of time be required, Applicant hereby petitions for same and requests that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 503182** unless paid for concurrently via EFS-Web.

Customer Number: **33,794**

Respectfully Submitted,

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Attorney for Applicant(s)

Date: January 16, 2012